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Abstract: Ipilimumab is approved for adjuvant melanoma treatment at a dose of 10 mg/kg, but its use is limited owing to high toxicity and treatment-associated costs. We retrospectively analyzed 29 patients who underwent complete resection of stage IIC–III melanoma and were treated with ipilimumab 3 mg/kg in an adjuvant setting. The aim was to assess development of adverse events (primary endpoint) and to evaluate survival outcomes (secondary endpoint) under adjuvant treatment with ipilimumab in a real-life setting. Immune-related adverse events (irAE) of all grades were reported in 72.4% of patients, grade 3 in 5.3% (n=2), and none for grade 4 or 5. Immune-related hypophysitis resolved in 3/8 (37.5%) and immune-related thyroiditis in 7/10 (70%) cases, whereas the others remained on substitution drugs. The rest irAEs affected the gut (n=8), skin (n=5), liver (n=2), and uvea (n=2) and resolved completely. Only one patient required tumor necrosis factor- owing to grade 3 colitis. Hospitalization was required in five cases owing to irAE (four colitis and one hypophysitis). At a median follow-up of 9.7 (1.7–16.8) months, 65.5% of the patients were free of disease. Median progression-free survival was 15.1 months, and median overall survival was not reached yet. Ipilimumab 3 mg/kg for the adjuvant treatment of high-risk patients with fully resected melanoma favors a better safety profile compared with the approved dose of 10 mg/kg in the same setting. Although its limited application owing lately promising data of antiprogrammed cell death protein-1 treatment, it may be considered as additional option or second-line treatment after fully resected disease recurrence under antiprogrammed cell death protein-1 treatment.

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Ipilimumab is approved for adjuvant melanoma treatment at a dose of 10 mg/kg, but its use is limited owing to high toxicity and treatment-associated costs. We retrospectively analyzed 29 patients who underwent complete resection of stage IIC–III melanoma and were treated with ipilimumab 3 mg/kg in an adjuvant setting. The aim was to assess development of adverse events (primary endpoint) and to evaluate survival outcomes (secondary endpoint) under adjuvant treatment with ipilimumab in a real-life setting. Immune-related adverse events (irAE) of all grades were reported in 72.4% of patients, grade 3 in 5.3% ($n = 2$), and none for grade 4 or 5. Immune-related hypophysitis resolved in 3/8 (37.5%) and immune-related thyroiditis in 7/10 (70%) cases, whereas the others remained on substitution drugs. The rest irAEs affected the gut ($n = 8$), skin ($n = 5$), liver ($n = 2$), and uvea ($n = 2$) and resolved completely. Only one patient required tumor necrosis factor-α owing to grade 3 colitis. Hospitalization was required in five cases owing to irAE (four colitis and one hypophysitis). At a median follow-up of 9.7 (1.7–16.8) months, 65.5% of the patients were free of disease. Median progression-free survival was 15.1 months, and median overall survival was not reached yet. Ipilimumab 3 mg/kg for the adjuvant treatment of high-risk patients with fully resected melanoma favors a better safety profile compared with the approved dose of 10 mg/kg in the same setting. Although its limited application owing lately promising data of antiprogrammed cell death protein-1 treatment, it may be considered as additional option or second-line treatment after fully resected disease recurrence under antiprogrammed cell death protein-1 treatment.

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Introduction

Melanoma shows rising incidence rates worldwide, exhibiting the highest rates in Australia, New Zealand, and Switzerland [1]. Although the incidence rates of most common cancer types have decreased during the past decades, melanoma incidence rates have increased continuously, affecting virtually all age classes [2]. Fair skin type and extensive intermittent UV radiation are well-known risk factors [3]; however, melanoma can affect virtually any individual with the combination of specific oncogene mutations [4].

Despite the excellent survival of early stages [5], advanced stages imply a poor prognosis if left untreated. Patients with stage III melanoma show high heterogeneity with 10-year survival rates of 88–24% depending on the subcategory of the stage III types: stage IIIA reveals a 10-years overall survival (OS) rate of 88%, IIIB of 77%, IIIC 60%, and IIID of 24%. Although the prognosis of stage IIA and B presents a 10-years OS of 82–88%, that of stage IIC declines to 75% [5].

To save patients from progression into stage IV disease, different adjuvant treatment settings have been implemented for patients at risk for progression: interferon-α achieved an 8% improvement of 10-year OS in patients with melanoma with micrometastases in the sentinel lymph node biopsy and ulcerated primary tumors [6]. Comparison of high-dose versus low-dose or intermediate-dose interferon could not prove superior efficacy but was accompanied with stronger and more severe adverse events (AEs) [7]. Other treatment strategies such as high-dose interleukin-2 was not convincing in improvement of OS [8].

Ipilimumab is a fully human IgG1 monoclonal antibody that blocks the cytotoxic T lymphocyte-associated antigen 4. It achieved Food and Drug Administration (FDA) approval for stage IV disease in 2011 at a dosage of 3 mg/kg. AEs comprise mainly autoimmune toxicity against organs such as pituitary gland, gut and liver system, lung, and thyroid glands among others, and are treatment related, that is, 37 versus 18% for 10 versus 3 mg/kg dosage in advanced stages. Most of these AEs are related to diarrhea or colitis (10 vs. 6%), hepatitis (3 vs. 1%), or hypophysitis (3 vs. 2%) [9]. Application in an adjuvant setting for

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patients with stage III melanoma at a dosage of 10 mg/kg resulted in higher rates of recurrence-free survival (RFS) (40.8 vs. 30.3%) and OS (65.4 vs. 54.4%) compared with placebo in the adjuvant setting [10]. Approval from the US FDA was gained for this population at this dose as provided in the approval study in 2015 [10]. However, mainly owing to high toxicity and high treatment-associated costs, ipilimumab was not reimbursed in Europe or Australia for the adjuvant treatment of melanoma in the aforementioned schedule.

In this context, we applied adjuvant ipilimumab in the conventional treatment dose of 3 mg/kg every 3 weeks in patients with high-risk melanoma after complete lymph node resection or excision of in-transit disease during October 2016 and May 2017. In the following sections, we present our real-life experience data using this treatment modality.

Patients and methods

Patient's selection and data acquisition

We conducted a single-center retrospective study with patients with stage IIC–III melanoma who were treated with adjuvant ipilimumab at the Dermatology Department of the University Hospital Zurich between October 2016 and May 2017. Stage III disease was subclassified as IIIA, IIIB, or IIIC according to the American Joint Committee on Cancer 7th ed. Patients had to have at least one cycle of ipilimumab for being qualified for the analysis. Ipilimumab was administered intravenously at a dose of 3 mg/kg every 3 weeks for a maximum of four cycles based on the reimbursed protocol for stage IV disease. Eligible patients required complete lymphadenectomy or complete resection of in-transit disease within 12 weeks before the first infusion of ipilimumab. Evaluation of disease was radiologically performed with PET/computed tomography scans every 12 weeks.

Treatment was not applied in pregnant or breastfeeding women and in patients with an active severe autoimmune disease, excluding Hashimoto thyroiditis. Treatment had to be stopped and adapted in case of disease progression.

Demographical and clinicopathological parameters and data on disease course of eligible patients were collected by reviewing patients' electronic medical files. AE were documented with the use of the Common Terminology Criteria for Adverse Events version 4.03. Resolution of an immune-related adverse event (irAE) was defined as an improvement to grade 1 or less. OS was defined as the length of time in months from treatment start to either death or last follow-up (analysis accounted for censored survival times). Progression-free survival (PFS) was defined as the length of time in months from treatment start until to progression or recurrence or melanoma-related death. Local ethics committee approved, as well as written informed consent for tissue storage, including retrospective analysis, with collection of clinical/laboratory/histological information before collection was obtained (KEK-ZH-Nr. 647, 800).

Primary end point of the study analyzed quality and quantity as well as onset of AEs under adjuvant ipilimumab in a real-life setting. Secondary end point addressed survival outcomes (median OS and PFS) following treatment initiation. Moreover, we performed a systematic literature research and compared our study cohort with available prospective or retrospective trials to evaluate whether the incidence of AES of our cohort is similar to that reported in the literature.

Statistical analysis

Statistical analysis of the data was performed using GraphPad Prism software version 7.0 (GraphPad Software, San Diego, California, USA). Kaplan–Meier survival curves were performed using log-rank test. Statistical analysis was done using descriptive analysis. *P* values of less than 0.05 were considered statistically significant.

Results

We retrospectively treated 29 (14 females and 15 males) patients with a median age of 52.4 (range: 15.4–76.1) years. One (3.45%) patient had stage IIC melanoma, seven patients had stage IIIA (24.14%), 10 (34.48%) patients had stage IIIB, and 11 (37.93%) patients had stage IIIC melanoma. Twenty-one (72.41%) patients completed the set of four infusions of ipilimumab, six patients received three infusions (20.70%), one patient two infusions (3.45%), and another patient one cycle (3.45%).

The mean number of treatment cycles were 3.59 (3.29–3.88, SD: 0.78). Mean days of treatment duration was 54.48 (48.12–60.85, SD: 16.74). Discontinuation rate was 27.58% (8 of 29 patients). Treatment was stopped in patient 15 owing to the patient's request. Patient 22 received only two and patient 25 only three doses of ipilimumab owing to disease progression (mentioned later). In the other patients, treatment was stopped owing to AE (mentioned later). For further details, please refer to Table 1 (Patients' characteristics).

Immune-related adverse events

In those 29 patients, 38 irAEs were reported during treatment with adjuvant ipilimumab (mean 1.31/patient). In total, 21 (72.4%) patients experienced at least one irAE, and only eight patients did not experience any irAE (27.59%): 16 (42.11%) irAEs were grade 1 and 20 (52.63%) were grade 2, whereas only two (5.26%) were grade 3 irAEs (Table 2). Autoimmune toxicities affected mostly thyroid ($n=10$, 26.32%) or pituitary glands (each $n=8$, 21.05%), gut system ($n=8$, 21.05%), and the skin ($n=6$, 15.79%). Skin AEs consisted of two (5.26%) events of pruritus, one (2.63%) mild erythema, and three (7.90%) cases of mild maculopapulous exanthema. Owing to the mild courses and rapid treatment response, no biopsies were taken. Increased pancreatic enzymes without further implication, uveitis, and hepatitis were detected in two (5.26%) cases each. However, the hepatitis in patient 16 cannot be clearly attributed to the ipilimumab treatment by itself, as the patient was elsewhere also treated with Traditional Chinese Medicine.

AQ7 **Table 1 Patients' characteristics**

Patients no.	Sex	Age	Melanoma type	Ulceration	Breslow index (mm)	Mutation status	Number of infusions	American Joint Committee on Cancer Stage	Type of metastases[a]	Metastases in SLNB[a]	Numer of metastases[a]	RECIST after treatment end		Follow-up until next treatment start (months)	Following treatment
												First follow-up	Last follow-up		
1	Female	68	NM	Yes	> 4	Unknown	3	IIIC	2	Macro	2	Free of disease	Free of disease	14.8	None
2	Male	58	NM	No	> 1 ≤ 2	Unknown	3	IIIB	1	None	1	Free of disease	Free of disease	15.9	None
3	Male	50	SSM	No	> 2 ≤ 3	Unknown	4	IIIA	2	Macro	1	Free of disease	Disease recurrence	9.7	Nivolumab; TVEC
4	Male	76	LMM	No	≤ 1	1, 5	4	IIIB	1, 2	No SLNB	1	Free of disease	Disease recurrence	10.1	Nivolumab
5	Male	59	CUP	NA	NA	1	4	IIIC	2	No SLNB	2	Free of disease	Free of disease	12.9	None
6	Male	35	NM	Yes	> 2 ≤ 3	1	4	IIIC	1, 2	Extranodal	1	Disease recurrence	Disease recurrence	16.8	Combi-i Studie CPDR001F2301; NCT02967692
7	Female	45	NM	Yes	> 2 ≤ 3	1	4	IIIC	1, 2	Micro	2	Free of disease	Free of disease	13.7	None
8	Female	35	NM	NA	> 1 ≤ 2	Unknown	4	IIIB	2	Macro	1	Free of disease	Free of disease	14.0	None
9	Male	60	CUP	NA		2	3	IIIB	1, 2	No SLNB	1	Free of disease	Free of disease	14.4	None
10	Male	52	SSM	No	> 1 ≤ 2	Unknown	3	IIIA	2	Micro	1	Free of disease	Free of disease	15.0	None
11	Female	71	CUP	NA	NA	3	4	IIIC	2	NA	2	Free of disease	Disease recurrence	14.8	Surgery
12	Male	47	SSM	No	> 1 ≤ 2	1	2	IIIB	1, 2, 3	None	2	Disease recurrence	Disease recurrence	3.3	Nivolumab/T-VEC ± Pembro (Masterkey 265)
13	Male	40	SSM	No	> 2 ≤ 3	2	4	IIIB	1, 3	None	2	Free of disease	Free of disease	12.8	None
14	Female	69	SSM	No	> 1 ≤ 2	1	4	IIIB	1	No SLNB	1	Free of disease	Free of disease	10.1	None
15	Female	45	Ex neavo	Yes	> 1 ≤ 2	Unknown	1	IIIB	2	Macro	1	Free of disease	Free of disease	3.9	None
16	Female	53	SSM	No	> 2 ≤ 3	Unknown	4	IIIA	2	Macro	1	Free of disease	Free of disease	13.6	None
17	Male	54	NM	No	> 2 ≤ 3	Unknown	4	IIIA	2	Macro	1	Free of disease	Free of disease	9.9	None
18	Female	51	SSM	No	> 4	Unknown	4	IIIA	1, 2	No SLNB	2	Disease recurrence	Disease recurrence	5.7	Surgery (lymphadenectomia, nivolumab
19	Female	67	CUP	NA	NA	3	4	IIIB	1, 3	No SLNB	1	Disease recurrence	Free of disease	3.6	Pembrolizumab
20	Male	66	SSM0	Yes	> 4	Unknown	4	IIC	2	None	0	Free of disease	Free of disease	9.3	None
21	Male	51	ALM	No	> 1 ≤ 2	2	4	IIIC	1, 2	None	2	Disease recurrence	Disease recurrence	5.3 (death)	Nivolumab; VP; CLXH254X2101
22	Female	72	NM	Yes	> 1 ≤ 2	1	2	IIIC	1	No SLNB	2	Disease recurrence	Disease recurrence	1.7	Nivolumab/T-VEC ± Pembro (Masterkey 265)
23	Female	73	Unclassifiable	NA	NA	2	4	IIIC	1	Lymph node: 0/1 (no SLNB)	0	Disease recurrence	Disease recurrence	5.9	Pembrolizumab
24	Female	32	SSM	No	> 1 ≤ 2	Unknown	4	IIIA	2	Macro	1	Free of disease	Free of disease	6.6	None
25	Female	67	NM	NA	> 1 ≤ 2	1	3	IIIB	3	Micro	2	Disease recurrence	Disease recurrence	1.8	BRAF/MEK-I (Tafinlar/Mekinist)
26	Male	35	SSM	No	> 1 ≤ 2	1	4	IIIC	2	Macro	2	Free of disease	Disease recurrence	9.6	Pembrolizumab
27	Male	49	NM	Yes	> 4	1	4	IIIC	2, 3	None	2	Free of disease	Free of disease	5.8	None
28	Male	40	Unclassifiable	Yes	> 2 ≤ 3	1	4	IIIC	3	Micro	2	Free of disease	Free of disease	7.7	None
29	Female	15	Unclassifiable	No	> 1 ≤ 2	1	4	IIIA	2	Macro	1	Free of disease	Free of disease	9.4	None

[a]At onset of treatment.

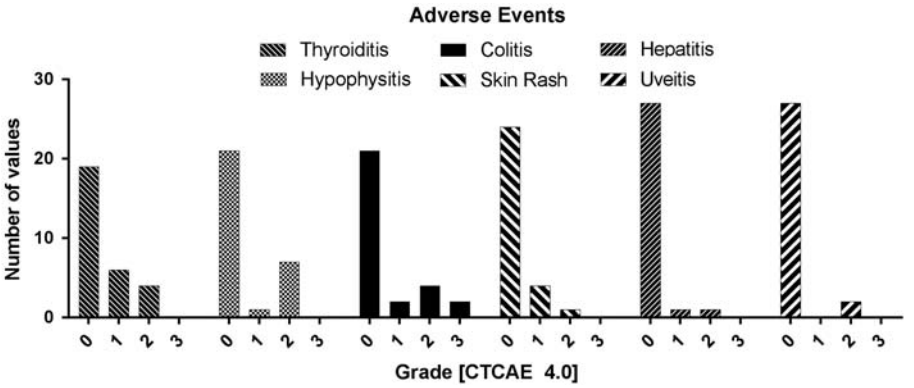
CR, complete response; NA, not available; PD, progressive disease type of metastases (owing to PET-computed tomography); PR, partial response: SLNB, sentinel lymph node biopsy; 1, in-transit/cutaneous; 2, locoregionale lymph nodes; 3, distant.

Table 2 Onset of adverse events

	Amount of AEs	Maximum grade	Onset (mean) (days)	AE resolution (%)	Resolution of AE (mean) (days)	Systemic steroids	Tumor necrosis factor-α	Hospitalization
Thyroiditis	10	2	55.2 (38–83)	70	85 (9–386)	0	0	0
Hypophysitis	8	2	76.0 (4–175)	37.5	219.5 (10–398)	7	0	1
Colitis	8	3	59.3 (5–106)	100	9.1 (2–21)	6	1	4
Skin rash	6	2	33.2 (8–62)	100	8.0 (5–14)	0	0	0
Hepatitis	2	2	97.0 (96–98)	100	84.5 (28–141)	0	0	0
Uveitis	2	2	124.0 (109–139)	100	45.0 (30–60)	1	0	0

AE, adverse events.

Fig. 1

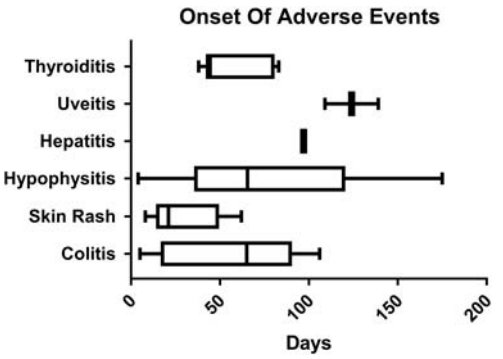


Immune-related adverse events differentiated by grades 0–3 following Common Terminology Criteria for Adverse Events (CTCAE) 4.03.

The same applies to patient 19, who was treated with TVEC ± and pembrolizumab before the ipilimumab treatment in the setting of the Masterkey-265 trial. Therefore, hypophysitis and thyroiditis in this patient might have occurred in the context of accumulation of both checkpoint inhibitor agents. One patient experienced a mild reactivation of his known psoriasis arthritis even before the treatment start (grade 1) as his hitherto treatment with infliximab had to be stopped before treatment with ipilimumab. Therefore, we did not include him into the statistics of irAE. We observed no pneumonitis, nephritis, nor cardiac involvement in our patient population. There were further no noteworthy other or new AEs recorded than the aforementioned irAEs.

Skin was the first affected organ (mean: 6.3 weeks), followed by pancreas (mean: 6.8 weeks), thyroid gland (mean: 7.5 weeks), gut system (mean: 8.5 weeks), and pituitary gland (mean: 10.9 weeks). Hepatitis occurred with a mean delay of 13.9 weeks, and uveitis with a delay of 17.7 weeks (Figs 1 and 2 and Table 2). The highest grade of irAE was related to colitis (grade 3), whereas other irAEs manifested with grade 2 at most – besides the pancreas, which achieved only grade 1 irAE. Duration of the irAE is presented in Table 2. It was foremost highest in hypophysitis (mean: 219.5 days), of which most did not recover (62.5%), followed by thyroiditis (mean: 85 days), with only three patients requiring levothyroxine. Mean duration of AEs in uveitis was 45 days, followed by colitis (mean: 9.1 days) and skin rash (mean: 8 days).

Fig. 2



Onset of immune-related adverse events.

Treatment of immune-related adverse events

Systemic steroids were required in 41% of the treated patients ($n=12$), accounting for 30% of all irAEs (15 cases of 50 recorded irAEs). Taken together, 24% of the treated patients required systemic steroids owing to hypophysitis ($n=7$), 21% owing to colitis ($n=6$), and 3% owing to uveitis ($n=1$). Cutaneous AEs were treated with topical therapy consisting of class III steroids and

polidocanol, 5%. No systemic steroids were required in all of these cases.

Hospitalization was required in five patients owing to irAE (17.24% of all patients): in four patients owing to colitis and in the other owing to hypophysitis. Tumor necrosis factor-α in combination with systemic steroids was necessary in one patient with pancolitis; in six patients with colitis, systemic steroids were sufficient; and the one patient with colitis did not require any systemic anti-inflammatory treatment at all.

Levothyroxine substitution was needed in two patients for bridging until reconstitution of the thyroid glands. Hydrocortisone substitution was necessary in seven of eight (87.5%) patients with hypophysitis; only one patient did not require specific treatment for reconstitution of the pituitary gland (12.5%). In six (75%) of these patients with hypophysitis, hydrocortisone treatment is still ongoing until today.

Resolution of adverse events

Ipilimumab was discontinued in six patients owing to AEs (6/29) (20.6%); in one patient after one, in another patient after two, and in four patients after three cycles of ipilimumab.

All irAEs affecting the gut system, skin, liver, uvea, and pancreas resolved completely after treatment of irAE and/or pausing ipilimumab treatment. Thyroiditis was not recovered in three of 10 (30%) cases and hypophysitis in five of eight (62.5%) cases.

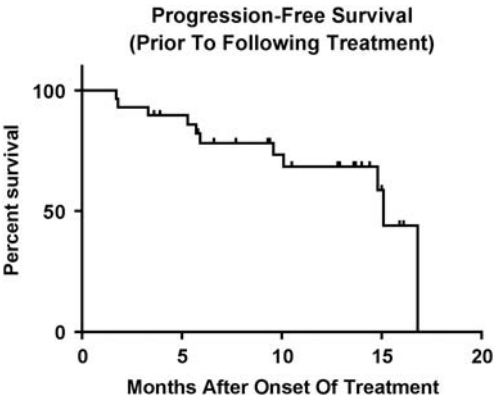
Taken together, six irAEs resulted in a durable damage (15.80% of all irAE), where five of these related to the pituitary gland (13.56% of all irAE), and one to the thyroid gland (2.63% of all irAE) of a patient who experienced also durable damage of the pituitary gland. Interestingly, this patient was afterward treated with nivolumab (patient 18).

Efficacy

At the first follow-up 3 months after treatment start, we recorded 19 (65.52%) patients free of disease and nine (31.03%) patients with a disease recurrence. At a median follow-up of 9.7 (1.7–16.8) months, 11 (37.93%) patients experienced disease recurrence, whereas 18 (62.07%) patients were free of disease. A 15-year-old child did not receive PET-computed tomography scans owing to the radiation exposure, but PET-MRI was done instead. Median PFS was 15.1 months, and median OS was not reached (Figs 3 and 4). One patient died 5.9 months after onset of treatment owing to disease progression, and 11 (37.93%) patients required subsequent treatment after disease progression (Table 1).

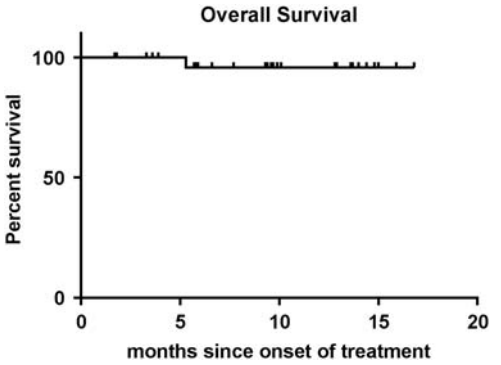
There was no correlation between disease recurrence and S100 ($P=0.498$) but a trend to higher lactate dehydrogenase levels at onset of treatment ($P=0.083$).

Fig. 3



Progression-free survival (before adjacent treatment).

Fig. 4



Overall survival (before following treatment).

Patients who had to quit treatment preterm owing to irAE did not have a higher incidence of disease relapse ($P=0.385$). Altogether, there was no correlation of grade of irAE and disease recurrence ($P=0.183$).

Discussion

To the best of our knowledge, this analysis represents the first report to assess the safety profile and efficacy of adjuvant ipilimumab in real-setting data in the aforementioned dosage.

In this retrospective single-center study involving patients with fully resected high-risk melanoma, 72.4% (21/29) of the patients under adjuvant ipilimumab at an intermediate-dose of 3 mg/kg (ipi3) administered every 3 weeks for the maximum of four cycles experienced at least one irAE.

We applied a different dosage schedule of ipilimumab than the one that has been FDA approved in the adjuvant setting, which definitely aggravates direct comparison with the current literature data. However, given the

Table 3 Comparison of adverse events in adjuvant ipilimumab treatment with literature

Dosage/clinical trial protocol	Ipi3 4c/3we (real-life)	Ipi10 (Checkmate 238)	Ipi10 (Checkmate 029)	Ipi3 (E1609)
All grade AEs (%)	72.4	98.5	90.4	98.6
Grade 3–4 (%)	7	45.9	41.6	36
Treatment discontinuation due to AEs	20.6	42.6	NA	35.2

AEs, adverse events; ipi3, ipilimumab 3 mg/kg; c, cycles; 3/we, every 3 weeks; ipi10, ipilimumab 10 mg/kg; NA, not available.

high toxic effects and cost of treatment with 10 mg/kg, justified questions have been raised whether ipilimumab should be given at a dose of 10 mg/kg or lower. Based on an unplanned analysis of the ECOG 1609 trial, which evaluates 1 year of treatment with ipi3, ipilimumab at 10 mg/kg (ipi10), or high-dose interferon, no substantial differences in PFS for patients treated with 3 mg/kg compared with 10 mg/kg were noted [11]. In our study cohort, patients with micrometastatic disease in sentinel lymph node biopsy underwent complete lymphadenectomy before scheduled adjuvant treatment. Complete lymphadenectomy was also mandatory in all adjuvant trials to date. Taking into account the results of the Multicenter Selective Lymphadenectomy Trial-II and the Dermatologic Cooperative Oncology Group trial [12, 13], complete lymphadenectomy is not associated with an OS benefit. Although adjuvant therapy seems reasonable in the subgroup of patients who are not undergoing a completion lymph node dissection, data from clinical trials are currently missing for this recommendation.

Ipilimumab is known to exert irAEs in both the intermediate-dose of 3 mg/kg and in the high-dose of 10 mg/kg in the advanced disease stages [14,15]. Severe irAEs have been reported to be dose dependent and occur frequently under combination immunotherapy with ipilimumab and nivolumab [9,16].

According to ECOG 1609 again, 36% of the analyzed patients with ipi3 experienced grade 3 irAEs [11], whereas only 7% (2/29) grade 3 AEs were noticed in our study. Moreover, none of our patients experienced a grade 4 AE. However, interpretation of this difference has to be made carefully owing to the small number of our study cohort. In the recent published study of ipi10 versus nivolumab 3 mg/kg in the adjuvant setting, 98.5% of patients experienced at least one AE in the ipilimumab group; grade 3 or 4 AEs were reported in 45.9% [17]. Similar irAE rates were reported in the Checkmate 029 trial of ipi10 versus placebo (all grade irAE 90.4, grade 3–4 41.6%) [10]. On the contrary, only 72.4% of our study cohort experienced at least one irAE with the mean cycle duration being 3.59, highlighting the better tolerability of the aforementioned dosage schedule underlying the dose-related toxicity. Most common irAEs experienced with ipi10 were the following: 63% skin toxicities, 46% gastrointestinal-toxicities, 24.4% hepatitis, 37.8% endocrine, and 16.3% of hypophysitis [17]. Conversely, we report on lower AE rates with ipi3: 15.79% skin, 21.05 gastrointestinal, 5.26% hepatitis, and 26.32% endocrine toxicities. Although direct comparison cannot be made (retrospective vs. prospective multicenter design and different dosages), the differences in AEs are unquestionable (Table 3).

The rate of AEs in our study that led to the treatment discontinuation was 20.6% (6/29), being definitely less than the 42.6% reported with ipi10, though higher than the 5% reported in the Checkmate 209–238 trial with adjuvant nivolumab (Table 3) [10,17]. Compared with stage IV disease with ipi3, where only 63% of patients experienced at least one irAE, we report on higher AE rate of any rate in the adjuvant setting [9]. This could be explained by the different immunity in stage III patients leading to higher AE rates in adjuvant setting. It is known that both anti-cytotoxic T lymphocyte-associated antigen 4 and antiprogrammed cell death protein-1 (PD-1) antibodies induce CD8+ effector memory T-cells, which then play an important role not only for immune surveillance but potentially also for the development of irAEs [18].

Two patients experienced grade 2 uveitis under adjuvant ipilimumab. The symptoms have slowly improved under steroid treatment and were completely resolved. Ocular irAE are very rare and have been reported in less than 1% of patients receiving ipilimumab. As stated in a systemic review of 11 clinical trials and 4965 patients, the incidence of uveitis ranged from 0.3 to 6% [19]. No incidence of uveitis was recorded in the EORTC 18071 trial with ipi10 [20].

The rest of the observed irAEs involved skin, gastrointestinal tract, and endocrine organs and were easily managed, with only one patient requiring, substantial to steroid treatment, therapy owing to colitis. Moreover, most irAEs resolved in accordance with the established management guidelines with the exception of the patients who experienced endocrinopathy and hypophysitis, who continue to take replacement therapy.

Interestingly, 62.1% of our study population (18/29) were free of disease at last follow-up (median follow-up time: 9.7 months), whereas only one patient died owing to rapid disease progression within 5.9 months after treatment onset. Similar RFS rates (60.8%) were reported within the Checkmate-238 study with ipi10 at 12-month follow-up [17]. The ECOG 1609 trial demonstrated no difference in RFS in ipi3 and ipi10 (54% with ipi10 and 56% with ipi3) at 3.1-year follow-up [11]. In the same study and at 12-month follow-up, RFS rates with ipi3 were 70%; this 8% numerical difference compared with our RFS rates could be explained by the low number of patients included in our study. It is clear that owing to

limitations such as the retrospective study design, short follow-up time, and small number of patients, none of the conclusions regarding the efficacy of the administered ipilimumab protocol can be made.

Recently, nivolumab, a monoclonal IgG4 anti-PD-1, showed significant superior relapse-free survival (RFS) in a phase 3 clinical trial compared with ipilimumab (66.4 vs. 52.7%), with a hazard ratio (HR) of 0.65 ($P < 0.0001$), at 18-month follow-up [17]. Based on this finding, nivolumab gained FDA approval as an adjuvant treatment for patients with melanoma with high-risk for relapse. Similarly, and in the same setting, Keynote-054 met its primary end point with a RFS HR for pembrolizumab of 0.57 [21]. Along with these agents, inhibition of the MAPK pathway is an additional option in patients harboring a BRAF V600 mutation, owing to an exceptional activity with OS benefit and a 53% reduction for relapse with the combination of dabrafenib and trametinib (HR: 0.47; 95% confidence interval: 0.39–0.58; $P < 0.0001$) [22].

Conclusion

Taking into account the impressive new data in the adjuvant field, the substantial toxicity related to ipilimumab and the superior efficacy of nivolumab and pembrolizumab, the future of the former as monotherapy in any dosage schedule seems limited. As these results entirely affect the landscape of the adjuvant treatment, there seems to be limited application of ipilimumab in the aforementioned patient cohort. However, it can be concluded that ipi3 favors a better safety profile compared with the toxicity spectrum already defined for this drug at the currently approved dose of 10 mg/kg in the same setting, and therefore, it may be still considered as an additional option or second-line treatment option for fully resected melanoma in high-risk individuals after disease-recurrence during anti-PD-1 or kinase inhibitor treatment. Besides, its contribution as a synergic agent to anti-PD-1 in the adjuvant setting is being currently investigated in an ongoing clinical trial (NCT01844505).

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Conflicts of interest

Joana Mangana received travel grants from MSD and has intermittent advisory roles for Merck and Pfizer. She has received research grants from BMS outside the submitted work. Reinhard Dummer has intermittent, project-focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, and Sun Pharma outside the submitted work. For the remaining authors there are no conflicts of interest.

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